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Lansoprazole, a Novel Benzimidazole Proton Pump Inhibitor, and Its Related Compounds Have Selective Activity against *Helicobacter pylori*

TOMOYUKI IWAHI,[1]* HIROSHI SATOH,[1] MASAFUMI NAKAO,[1] TAMIKO IWASAKI,[1] TOSHIYUKI YAMAZAKI,[1] KEIJI KUBO,[1] TOSHIHIDE TAMURA,[2] AND AKIRA IMADA[1]

Research and Development Division, Takeda Chemical Industries, Ltd., 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532,[1] and Department of Bacteriology, Hyogo College of Medicine, Nishinomiya, Hyogo 663,[2] Japan

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The activities of various types of antiulcer agents against *Helicobacter pylori* (formerly called *Campylobacter pylori*) strains were determined by an agar dilution method. Among the compounds tested, two benzimidazole proton pump inhibitors, lansoprazole (AG-1749) and omeprazole, were found to have significant activities against this organism. The activity of lansoprazole was comparable to that of bismuth citrate, with MICs ranging from 3.13 to 12.5 μg/ml, and fourfold more potent than that of omeprazole. A major metabolite and two acid-converted rearrangement products of lansoprazole also exhibited good activities comparable or superior to that of the parent compound. Exposure to lansoprazole of *H. pylori* growing in a liquid medium led to an extensive loss of viability without a reduction in culture turbidity and produced an aberrant bacterial morphology characterized by the irregular constriction of cells and the collapse of cell surface structures. The antibacterial activity of lansoprazole and its related compounds was selective against *H. pylori*; common aerobic and anaerobic bacteria and *Campylobacter jejuni* were not inhibited by 100 μg/ml.

Helicobacter pylori (7), formerly known as *Campylobacter pylori*, is a microaerophilic, gram-negative, urease-positive, spiral or curved bacterium which was first isolated by Warren and Marshall in 1983 from the gastric mucosae of patients with gastritis (37). Since their report, numerous groups of investigators worldwide have shown that the distribution of *H. pylori* is highly associated with both gastritis and peptic ulcers (3, 9, 15, 20, 38), and Marshall et al. (17) and Morris and Nicholson (26) have reported that ingestion of *H. pylori* cultures induces gastritis in human volunteers. There are also several reports indicating that eradication of *H. pylori* by treatment with bismuth salts or bismuth-antibiotic combinations leads to a persistent improvement of gastritis and a lower relapse rate of peptic ulcers (4, 12, 16, 18, 23, 28, 29). Thus, it is now widely accepted that *H. pylori* is an important human pathogen causing type B gastritis of stomachs and probably a major predisposing cause of duodenal ulcers.

Taking a close association between *H. pylori* and gastroduodenal disorders into consideration, we examined the activities against this organism of various types of antiulcer agents, including lansoprazole (AG-1749), a novel benzimidazole proton pump inhibitor (27, 31), by an agar dilution method. In this report, we show that the benzimidazole proton pump inhibitors have a notable and selective activity against *H. pylori* and that the activities of lansoprazole and its related compounds are comparable or superior to that of a bismuth salt known to posess a reliable activity against this organism (1, 8, 22, 36). The effect of lansoprazole on the growth kinetics and morphology of *H. pylori* growing in a liquid medium was also investigated.

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* Corresponding author.

MATERIALS AND METHODS

Antiulcer agents. Lansoprazole, its derivatives, and omeprazole were synthesized by Takeda Chemical Industries, Ltd., Osaka, Japan. Samples of ranitidine (mp, 152 to 153°C) and famotidine (mp, 165 to 167°C) were obtained by extracting them from Zantac (Glaxo Laboratories, Toronto, Canada) and Gaster (Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan), respectively, and purifying them in our division. Cimetidine and bismuth citrate were purchased from Sigma Chemical Co., St. Louis, Mo., and Mitsuwa Chemical Co., Osaka, Japan, respectively. All of the compounds were dissolved or suspended in dimethyl sulfoxide at a concentration of 10 mg/ml and then diluted in distilled water to give the desired concentrations.

Bacterial strains. *H. pylori* NCTC11637 (type strain) and NCTC11916 were kindly provided by B. J. Marshall, Royal Perth Hospital, Perth, Western Australia, Australia, through the initiative of one of us (T.T.). Of 15 *H. pylori* isolates, nine strains (CPY0011-1, 0164, 0232, 0241, 0252, 0262, 0291, 0303, and 0311) were kindly supplied by T. Nakazawa (School of Medicine, Yamaguchi University, Yamaguchi, Japan), two strains (PCL56 and PCL67) were from T. Itoh (Tokyo Metropolitan Research Laboratory of Public Health, Tokyo, Japan), and the remaining four strains (CLO1, CLO4, CLO6, and KS13) were recovered from human gastric biopsy specimens by one of us (T.T.) in Hyogo College of Medicine, Hyogo, Japan. The identification of clinical isolates was based on standard biochemical tests (19). Stock cultures were stored at −80°C in brucella broth (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 2.5% heat-inactivated fetal bovine serum (FBS) and 15% glycerol. The serum was heat inactivated at 56°C for 30 min prior to use. Clinical isolates of *Campylobacter jejuni* and laboratory standard strains of common aerobic and anaerobic bacteria were obtained from our culture collection.

Determination of MICs by the agar dilution method. *H.*

pylori and *C. jejuni* strains were grown on brucella agar (BBL) supplemented with 7% horse blood at 37°C for 3 days in GasPak jars (BBL) with Campy Paks (BBL) and suspended in brucella broth with 2.5% heat-inactivated FBS to give the turbidity equivalent to McFarland standard no. 1; this resulted in suspensions containing about 5×10^7 CFU/ml. The bacterial suspensions were applied to the brucella-blood agar plates containing twofold serial dilutions of antiulcer agents by a multipoint inoculator capable of delivering 1-μl samples. The plates were incubated at 37°C in a microaerobic environments. After 3 days of incubation, there was satisfactory growth of all strains tested on the control plates. Readings were done after 3 days unless otherwise specified. MICs were defined as the lowest concentrations of the test compounds inhibiting visible bacterial growth.

MICs for common aerobic and anaerobic bacteria were also determined by the agar dilution method. Trypticase soy agar (BBL) alone or supplemented with 10% bovine blood for aerobic bacteria and GAM agar (Nissui Seiyaku Co., Ltd., Tokyo, Japan) for anaerobic bacteria were used. The inocula were prepared in Trypticase soy broth (BBL) for aerobic bacteria and in GAM broth (Nissui) for anaerobic bacteria from overnight cultures and adjusted to give approximately 10^8 CFU/ml. Plates were incubated at 37°C for 20 h in an aerobic atmosphere for aerobic bacteria and in an aerobic glove box for anaerobic bacteria.

Determination of bacteriolytic and bactericidal actions. For the determination of bacteriolytic and bactericidal actions, a broth cultivation technique with a few modifications of the method proposed by Morgan et al. (25) was used. Because *H. pylori* requires adequate gas dispersion to produce good growth in liquid media (6), broth layers were set less than 3 cm in height in flat-bottom specimen containers, and the cultivation was done on a gyratory shaker at 150 rpm. The stock cultures of *H. pylori* strains were thawed at room temperature and inoculated into 140 ml of brucella broth with 2.5% heat-inactivated FBS in 500-ml sterile glass Erlenmyer flasks to give about 10^6 CFU/ml for the tests with large inoculum levels and about 10^5 CFU/ml for the tests with small inoculum levels. After 20 h of microaerobic incubation at 37°C with gyration, the culture was divided into 7.2-ml volumes in 16-cm^2 plastic square storage bottles (Nalge Co., Rochester, N.Y.), and a 0.8-ml volume of fresh medium or the test solution was added. The cultures were further incubated microaerobically at 37°C with gyration. At times from 0 to 24 h, 1-ml samples for turbidity determination and 0.2-ml samples for viability determination were taken. The turbidity was monitored at 570 nm in a Coleman JUNIOR II spectrophotometer (Coleman Instruments, Oak Brook, Ill.). The viability was enumerated by the plate count technique. Serial 10-fold dilutions were made in brucella broth with 2.5% heat-inactivated FBS, and a 0.01 ml portion of each, from neat to 10^7 dilution, was plated in duplicate onto brucella agar supplemented with 7% heat-inactivated horse serum. Colonies were counted after 3 days of incubation at 37°C under microaerobic conditions and were expressed in CFU per milliliter.

Electron microscopy. *H. pylori* NCTC11637 was grown and exposed to lansoprazole as for the bacteriolytic and bactericidal tests. The organisms from control and treated cultures were pre-fixed with 2.5% glutaraldehyde in 0.05 M cacodylate buffer (pH 7.4) for 3 h and postfixed with 1% osmium tetroxide in Kellenberger buffer (pH 6.1) for 2 h. The fixed cells were dehydrated with a graded series of ethanol. For scanning electron microscopy, the specimens were critical point dried, coated with platinum-palladium, and examined with an ISI-DS130 scanning electron microscope. For transmission electron microscopy, the specimens were embedded in Epon 812. Ultrathin sections were prepared with an LKB ULTROTOME III, doubly stained with uranyl acetate and lead citrate, and examined in a JEOL JEM-1200 EX transmission electron microscope. Negatively stained specimens of the control culture were prepared with 3% ammonium molybdate (pH 6.5) on Formvar-coated copper grids.

TABLE 1. Activities of various antiulcer agents against 17 strains of *H. pylori*

Agent	MIC (μg/ml)[a]		
	Range	50%	90%
Bismuth citrate	6.25–25	6.25	12.5
Cimetidine	800–>800	>800	>800
Ranitidine	>800	>800	>800
Famotidine	>800	>800	>800
Omeprazole	12.5–50	25	25
Lansoprazole	3.13–12.5	6.25	6.25

[a] MICs were determined by the agar dilution method on brucella agar with a bacterial suspension of about 5×10^7 CFU/ml. 50% and 90%, MICs for 50 and 90% of the strains.

RESULTS

Activities of antiulcer agents against *H. pylori*. The MICs of six antiulcer agents for 17 strains of *H. pylori* were determined by the agar dilution method. Table 1 shows the ranges of MICs and the concentrations required to inhibit 50 and 90% of the strains, which were determined after 3 days of incubation. All of the plates for the MIC tests were further incubated for 2 additional days, but there were no changes in the MICs. Bismuth citrate was active against all of the strains tested, and these MICs agree well with those previously reported by several investigators (8, 22, 36). Cimetidine, ranitidine, and famotidine were almost inactive, and these results are also in agreement with those reported elsewhere (8, 32). In contrast to these histamine H_2 receptor antagonists, two proton pump inhibitors, omeprazole and lansoprazole, showed considerable activities. The activity of lansoprazole was fourfold more potent than that of omeprazole and was comparable to that of bismuth citrate.

Activities of lansoprazole-related compounds against *H. pylori*. To confirm the notable activity of lansoprazole against *H. pylori*, we tested the activities of some lansoprazole-related compounds with a general formula (Fig. 1). Two partial structure analogs, 2-mercaptobenzimidazole and 2-hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine, showed only weak activities, with MICs ranging from 400 to 800 μg/ml, and their combinations showed only additive effects (data not shown). On the other hand, all of the

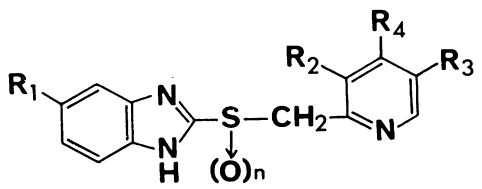

FIG. 1. General formula of substituted benzimidazoles.

TABLE 2. Comparative activities of various substituted benzimidazoles against *H. pylori*

Compound	Substituent					Range of MICs (μg/ml)[a]
	n	R_1	R_2	R_3	R_4	
Lansoprazole	1	H	CH_3	H	OCH_2CF_3	3.13–12.5
AG-1760	1	H	CH_3	H	$OCH_2CF_2CF_3$	1.56–6.25
AG-1764	1	H	CH_3	H	$OCH_2CF_2CF_2H$	0.78–6.25
AG-1788	1	H	CH_3	H	$OCH_2(CF_2)_3CF_2H$	1.56–6.25
AG-1777	0	H	CH_3	H	OCH_2CF_3	3.13–25
AG-1776	0	H	CH_3	H	$OCH_2CF_2CF_3$	0.78–1.56
AG-1789	0	H	CH_3	H	$OCH_2CF_2CF_2H$	0.78–3.13
AG-1787	0	H	CH_3	H	$OCH_2(CF_2)_3CF_2H$	1.56–3.13
AG-1605	0	H	H	H	$OCH_2CH(CH_3)_2$	6.25–25
AG-1604	0	CF_3	H	H	$OCH_2CH(CH_3)_2$	12.5–25
AG-1591	0	CF_3	H	H	$OCH(CH_3)_2$	12.5–25
Omeprazole	1	OCH_3	CH_3	CH_3	OCH_3	12.5–50

[a] MICs against 7 to 17 strains of *H. pylori* were determined by the agar dilution method on brucella agar with a bacterial suspension of about 5×10^7 CFU/ml.

substituted benzimidazole derivatives having a pyridine ring exhibited significant activities, although there were considerable differences in the degrees of their activities (Table 2). Structure-activity relationship studies indicated that the antibacterial activities of the substituted benzimidazoles were predominantly related to the nature of the substituents at the no. 4 position of the pyridine ring; all of the compounds with fluoroalkoxy substituents demonstrated activities several times more potent than those of the compounds with alkoxy groups, and some of compounds were found to be more active than lansoprazole. The oxidation of the sulfur atom between the benzimidazole and 2-methylpyridine had little influence on the antibacterial activity. Thus, one of the metabolites of lansoprazole, AG-1777 (12a), gave an activity comparable to that of the parent compound.

As it has been proposed that lansoprazole is converted readily into its active forms (Fig. 2) within the acidic compartment of gastric parietal cells and that these acid-converted active forms exert inhibition of a proton pump (27), we also tested the activities of two acid-converted

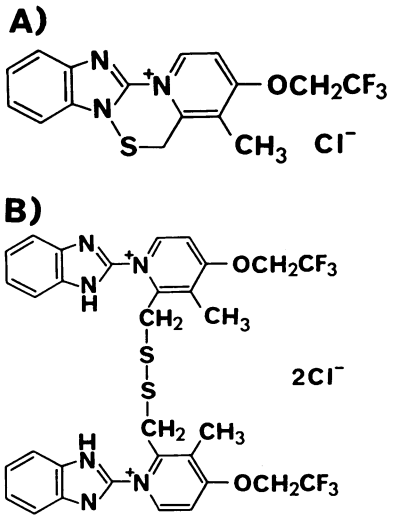

FIG. 2. Chemical structures of AG-2000 (A) and AG-1812 (B).

TABLE 3. Activities of acid-converted forms of lansoprazole against 11 strains of *H. pylori*

Compound	MIC (μg/ml)[a]		
	Range	50%	90%
AG-2000	0.78–3.13	3.13	3.13
AG-1812	0.78–3.13	1.56	3.13

[a] MICs were determined by the agar dilution method on brucella agar with a bacterial suspension of about 5×10^7 CFU/ml. 50% and 90%, MICs for 50 and 90% of the strains tested.

rearrangement products of lansoprazole, AG-2000 and AG-1812, against *H. pylori* (Table 3). AG-2000 and AG-1812 were two- to fourfold more active than lansoprazole.

Effects of lansoprazole on growth of *H. pylori* in a liquid medium. Bacteriolytic and bactericidal actions of lansoprazole were examined by monitoring the culture turbidity and viability in the broth cultures with relatively large inoculum levels. Figure 3 shows representative patterns obtained with strain NCTC11637 exposed to 6.25 (1× MIC), 25 (4× MIC), and 100 (16× MIC) μg of lansoprazole per ml. The cultures exposed to lansoprazole displayed marked inhibitions of growth at concentrations of 25 μg/ml or more as monitored turbidmetrically, but reductions in culture turbidity due to bacteriolysis were not observed at any concentration. On the other hand, the results of viability tests showed that lansoprazole possessed clear bactericidal action at 25 μg/ml or more; in the cultures exposed to 100 μg of lansoprazole per ml, 3-log reductions in the number of CFU per milliliter were observed in 6 h, and no visible organisms were detected in 24 h. The loss of viability without a reduction in culture turbidity was also observed with strains NCTC11916, CLO1, CLO4, and PCL56 exposed to 100 μg of lansoprazole per ml, although there were some differences among the strains in the degree of the loss of viability.

The bactericidal actions of lansoprazole against *H. pylori* strains were slightly more striking in the broth cultures with smaller inoculum levels (Table 4). In the cultures of all strains tested, no visible organisms were detected in 6 or 24 h at a concentration of 100 μg/ml.

Morphological changes of *H. pylori* cells exposed to lansoprazole in a liquid medium. The morphological changes of *H. pylori* NCTC11637 cells exposed to 100 μg of lansoprazole per ml for 6 h were examined by scanning and transmission electron microscopy in comparison with the morphology of untreated control cells (Fig. 4 and 5).

The control cells appeared as slightly curved bacilliforms, 2.0 μm long and 0.5 μm wide, with bluntly rounded ends, and some of the cells had two or more unipolar, sheathed flagella. The unit membranes of cell walls adhered closely to the underlying cytoplasmic membranes, and prominent electron-dense glycocalyx- or capsulelike structures external to the cell wall unit membranes were also often observed. These morphological features were consistent with those described for *H. pylori* cells in shaken broth cultures by Goodwin and colleagues (1, 6).

In contrast to the untreated control cells, most of the lansoprazole-treated cells appeared as atypical bacilliforms with cell surface defects, and occasionally rounded forms were also observed. Transmission electron microscopy confirmed the development of focal cell wall blebs and of free membranous vesicles arising as apparent extrusions of the cell wall structures and the occurrence of marked constrictions of bacterial cells.

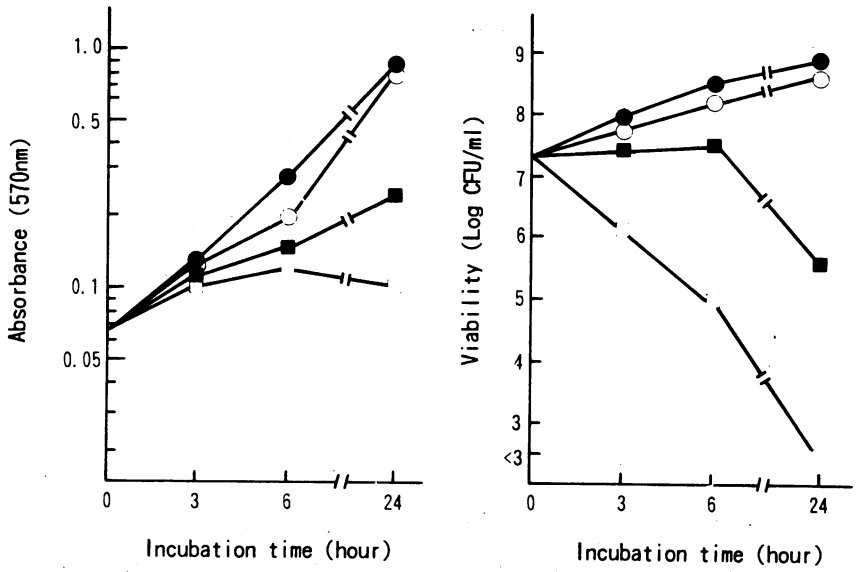

FIG. 3. Effect of lansoprazole on the growth of *H. pylori* in a liquid medium. *H. pylori* NCTC11637 was cultured microaerobically in brucella broth with 2.5% heat-inactivated FBS at 37°C with gyration and exposed to lansoprazole at concentrations of 0 μg/ml (●), 6.25 μg/ml (○), 25 μg/ml (■), and 100 μg/ml (□). After further incubation, the culture turbidity and viability were determined at each time point.

Activities of lansoprazole and its related compounds against *C. jejuni* and common aerobic and anaerobic bacteria. The activities of lansoprazole, AG-1777, AG-2000, and AG-1812 against other common bacteria were tested by the conventional agar dilution method. Lansoprazole and all of the related compounds tested had no activities at 100 μg/ml against 27 clinically isolated strains of *C. jejuni* and laboratory standard strains of other microorganisms, such as *Staphylococcus aureus* FDA209P, 308A, and 1840; *Streptococcus pyogenes* E-14 and S-8; *Streptococcus pneumoniae* types 1, 2, and 3; *Enterococcus faecalis* IFO3989; *Escherichia coli* NIHJ JC-2, O-111, GN5249, and T7; *Klebsiella pneumoniae* DT and no. 27; *Citrobacter freundii* IFO12681, TN474, and TN518; *Enterobacter cloacae* IFO12937, TN583, and TN618; *Serratia marcescens* IFO12648 and TN66; *Proteus vulgaris* IFO3988 and GN4712; *Proteus mirabilis* IFO3849; *Morganella morganii* IFO3168 and GN5278; *Pseudomonas aeruginosa* IFO3455, U31, P9, GN3407, and B184; *Peptostreptococcus anaerobius* B-30 and B-38; *Clostridium perfringens* CW-2 and 0668; *Lactobacillus acidophilus* IID-893; *Eubacterium alactolyticum* 1441; *Eubacterium limosum* ATCC 8486; *Bifidobacterium bifidum* AE-319; *Bacteroides fragilis* 2509, 2537, 1115, and 1117; *Fusobacterium nucleatum* MO-8; and *Fusobacterium mortiferum* 15 (data not shown).

TABLE 4. Bactericidal activity of lansoprazole against five strains of *H. pylori*[a]

Strain	Concn of lansoprazole (μg/ml)	Viability (log CFU/ml) at:			
		0 h	3 h	6 h	24 h
NCTC11637	0	6.2	6.6	7.0	8.9
	6.25		6.6	6.8	7.3
	25		6.3	6.4	4.8
	100		6.0	≤3.0	≤3.0
NCTC11916	0	6.2	6.5	6.9	8.5
	6.25		6.5	6.7	8.4
	25		6.5	6.4	7.3
	100		6.3	4.5	≤3.0
CLO1	0	6.2	6.6	7.0	8.5
	6.25		6.6	6.9	7.8
	25		6.5	6.7	6.0
	100		6.2	5.1	≤3.0
CLO4	0	6.5	6.7	7.3	9.2
	6.25		6.7	7.3	8.4
	25		6.6	6.9	6.3
	100		6.4	5.0	≤3.0
PCL56	0	6.6	6.9	7.2	9.0
	6.25		6.8	7.0	7.3
	25		6.8	6.7	≤3.0
	100		4.9	≤3.0	≤3.0

[a] *H. pylori* strains were cultured microaerobically in brucella broth with 2.5% heat-inactivated FBS at 37°C with gyration and exposed to various concentrations of lansoprazole. At the indicated intervals, samples were taken to determine viability.

DISCUSSION

H. pylori is commonly isolated from human gastric mucosa, and lines of evidence indicate that it plays a major etiologic role in type B gastritis and that it also is closely associated with duodenal ulcers, although its etiologic role is not yet conclusive (3, 9, 15, 38). In this study, we found that two antiulcer agents with the ability to inhibit the proton pump mechanisms in gastric parietal cells, lansoprazole and omeprazole, showed marked in vitro activities against *H. pylori*. In particular, lansoprazole, recently developed (27, 31), was fourfold more active than omeprazole, and the in vitro activity of the former agent was comparable to that of bismuth salts, which are used as an antiulcer agent and are known to have antibacterial activity against this organism (1, 8, 22, 36). Mainguet et al. (14) and Biasco et al. (2) have reported that omeprazole treatment of patients with duodenal ulcer and positive cultures for *H. pylori* resulted in negative cultures immediately after the treatment, but these

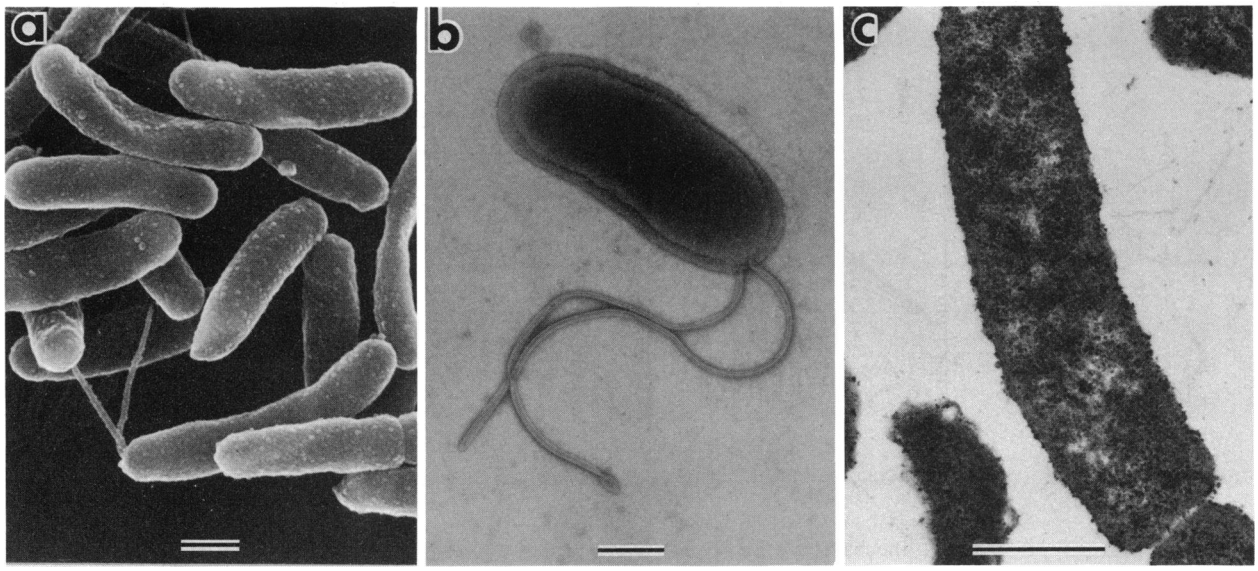

FIG. 4. Scanning (a), negative staining (b), and thin-section (c) electron micrographs of *H. pylori* NCTC11637 from a control 6-h culture in brucella broth with 2.5% heat-inactivated FBS at 37°C with gyration in a microaerobic environment. Bar, 0.5 μm.

investigators have not determined whether the efficacy of the drug is attributable to a direct action on the bacteria or to modifications of the intragastric content. To our knowledge, this is the first report suggesting the direct action of proton pump inhibitors against *H. pylori*.

While two partial structure analogs of lansoprazole, alone or in combination, showed only weak activities against *H. pylori*, the substituted benzimidazole derivatives possessing a pyridine ring displayed significant activities without exception. However, degrees of their activities varied considerably depending on the presence or absence of fluoroalkoxy groups at the C-4 position of the pyridine ring; the compounds with the fluoroalkoxy groups exhibited activities several times more potent than those of the compound without the groups. These findings indicate that the basic structure substituted with a pyridine ring plays an important role for the antibacterial activity and that an advantage of lansoprazole over omeprazole in antibacterial activity may be due to the presence of trifluoroethoxy group at the C-4 position of the pyridine ring.

It is shown elsewhere that (i) after oral administration of [^{14}C]lansoprazole, 37 and 67% of the total radioactivity are absorbed into the blood in rats and dogs, respectively, (ii) in their blood, a large amount of the radioactivity is found as

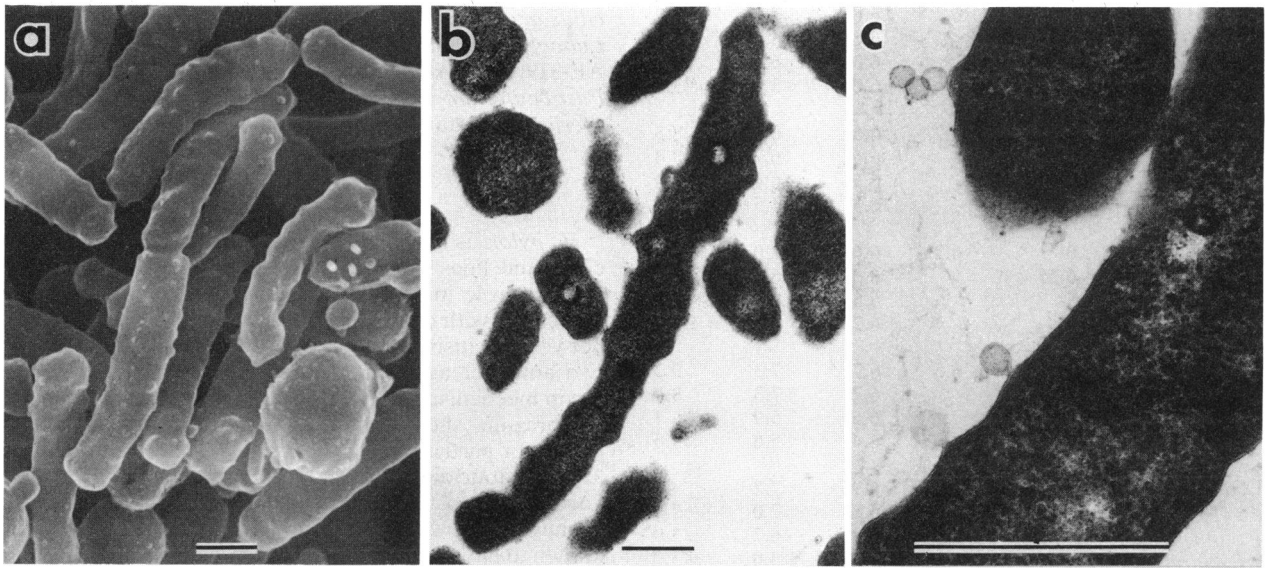

FIG. 5. Scanning (a) and thin-section (b and c) electron micrographs of *H. pylori* NCTC11637 exposed to 100 μg of lansoprazole per ml for 6 h in brucella broth with 2.5% heat-inactivated FBS at 37°C with gyration in a microaerobic environment. The bacillary profiles have irregular constrictions, and the development of focal cell blebs and of free membranous vesicles and the collapse of cell surface structures are shown. Bars, 0.5 μm.

several metabolites of lansoprazole with a small amount of the unchanged form, (iii) in rats given [^{14}C]lansoprazole orally, the radioactivity distributes in the gastric mucosa at a concentration several times higher than in the serum, and (iv) a main metabolite detected in rat gastric mucosa is AG-1777, and its concentration exceeds the level of the unchanged lansoprazole (12a). These findings suggest that lansoprazole and its metabolites may be transported not only locally but also via systemic circulation after absorption. Furthermore, it has been proposed that lansoprazole trapped by the gastric parietal cells is transformed to active compounds, such as AG-2000 and AG-1812, within the acidic compartment (27). Our MIC studies revealed that AG-1777, AG-2000, and AG-1812 also have good activities comparable or superior to that of the parent compound against *H. pylori*. Therefore, an oral dosing of lansoprazole may act both locally and systemically against *H. pylori* in the gastric mucosa of patients with gastroduodenal diseases.

Lansoprazole, though at concentrations several times higher than its MICs, showed marked bactericidal effects against *H. pylori* growing in shaken broth cultures. Associated with the lethal effect, some morphological abnormalities were observed by scanning and transmission electron microscopy; most of cells became irregularly constricted forms with cell surface defects. However, despite the drastic reductions in viability and the marked morphological alterations, there were no corresponding decreases in the turbidities of the treated cultures. Thus, lansoprazole appears to exert the loss of viability without cellular lysis (nonlytic death) against *H. pylori*. Armstrong et al. (1) have reported that although sequential endoscopic biopsy studies after an oral dosing of tripotassium dicitrato bismuthate revealed very rapid bacterial degradation and detachment from the epithelial surface membranes, the cultured organisms exposed to tripotassium dicitrato bismuthate in vitro exhibited no overt structural changes even at a relatively high concentrations, and the killing effect became manifest only after exposure for more than 8 h. In view of these observations, it is possible to speculate that the susceptibility of *H. pylori* to lansoprazole also may be modified by factors peculiar to the gastric environment.

One of the striking features of the antibacterial activities of lansoprazole and its related compounds is that these compounds were without activities against bacteria other than *H. pylori*. In general, the basis for the activity of an antibacterial agent is an interference with a biochemical mechanism unique to susceptible bacteria, and the spectrum of its activity reflects the taxonomic boundary. Therefore, the selective activity of lansoprazole and its related compounds against *H. pylori* indicates that this organism may have a peculiar biochemical mechanism(s) interfered with by these compounds. Furthermore, the lack of activity of these compounds against other common bacterial species may give the merits that lansoprazole after oral dosing does not create a severe risk of undesirable side effects due to changes in the intestinal flora and does not induce the acquisition of antibiotic resistance in other bacteria.

In vitro, a number of antibiotics, including β-lactams, macrolides, and quinolones, have been known to be highly active against *H. pylori* (1, 8, 10, 13, 22, 30, 32, 33, 36). However, when tested as single agents in clinical studies, erythromycin (23), doxycycline (35), ofloxacin (5), ciprofloxacin (34), and norfloxacin (24) have not succeeded in eradicating *H. pylori*. Failure of therapy and relapse have been common. The best results so far have been achieved with the combination of a nonabsorbed agent with topical activity, colloidal bismuth salts, and well-absorbed agents with systemic activity, amoxicillin and metronidazole (16, 18, 28, 29). On the basis of these findings, McNulty et al. (21) have suggested that the ideal antimicrobial agents for treating gastroduodenal disorders caused by *H. pylori* would be both locally and systemically active against this organism, be acid stable and amphoteric enough to penetrate into the gastric mucus and crypts where *H. pylori* is found (11), and cause little upset. Lansoprazole appears to fulfill almost all of these criteria. Thus, the activity of lansoprazole and its related compounds against *H. pylori* may give a benefit to the treatment with lansoprazole of gastroduodenal diseases.

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